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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/092,880	04/29/2002	Stephen J. Barenkamp	5127	2284

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SHOEMAKER AND MATTARE
Suite 1203
2001 Jefferson Davis Highway
Arlington, VA 22202-0286

EXAMINER
GRASER, JENNIFER E

ART UNIT	PAPER NUMBER
1645	10

DATE MAILED: 04/09/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
10/092,880	Barenkamp
Examiner	**Art Unit**
Jennifer Graser	1645

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Prel.Amendt A, 3/8/02, & Election 3/17/03*

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above, claim(s) *1-4, 6, 8, 9, and 14-20* is/are withdrawn from consideratio

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *5, 7, and 10-13* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☒ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☒ Certified copies of the priority documents have been received in Application No. *09/155,614* .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 7
18) ☐ Interview Summary (PTO-413) Paper No(s). _____
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

DETAILED ACTION

Election/Restriction

1. Applicant's election of Group II (claims 5-13) and the Species HMW2 in Paper No. 9 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). Claims 1-4 and 14-20 are hereby withdrawn from further consideration as they are drawn to a non-elected invention. Additionally, claims 6, 8, 9 and claim 12 (as it pertains to non-elected species HMW1, HMW3 and HMW 4) and claim 13 (as it pertains to HMW1) are also withdrawn from consideration as they are drawn solely to a non-elected species. They will not be considered unless a generic claim is allowed.

Claims 5, 7, 10, 11, 12 (only as claim 12 pertains to HMW2) and 13 (only as it pertains to HMW2) are currently under examination.

Priority

2. The status of the application as set forth in Preliminary Amendment A, filed 10/15/02, is incorrect. This application filed under former 37 CFR 1.60 lacks the necessary reference to the prior application. A statement reading "This is a Continuation-in-Part of Application No. 09/155,614, filed ." should be entered at the beginning of the paragraph under "References to Related Applications". Also, the current status of all nonprovisional parent applications referenced should be included.

Applicants have amended the specification to recite that this application is a 371 of PCT/US/9704707 04/10/97 which claims priority from application 08/617,697 4/01/96 which was a CIP or 08/302,832 09/16/94, which was a 371 of PCT/US93/02166 03/16/93, which claimed priority from British application GB 9205704.1 03/16/92.

However, it is noted that the instant claims contain subject matter which was first presented in application 08/617,697. The prior applications (08/302,832, PCT/US93/02166 and GB 9205704.1) contain no reference to monoclonal antibody AD6 or 10C5.

Accordingly, the instant claims are only granted priority back to application 08/617,697 which was filed 4/1/96. Applicants must point to and provide very specific evidence in the priority applications if they disagree with this finding.

Claim Rejections - 35 USC § 112

3. Claims 5, 7, 10, 11, 12 and 13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 5 is vague and indefinite because it does not describe the invention in a manner sufficient to satisfy the Statute's requirement of adequately describing and setting forth the inventive concept. Further, the name "HMW" is used for numerous different Haemophilus proteins. The claim should provide any structural properties, such as the amino acid sequence of the protein or molecular weight, which would allow for one to identify the protein without ambiguity. The mere recitation of a name does not adequately define the claimed protein.

Additionally, it is unclear what protein is encompassed by "any variant or fragment". The term "fragment" reads on as little as one amino acid.

Claim 7 is vague and indefinite due to the term "derived". The term "derived" does not provide the character or properties from the source that are to be retained in the final product, e.g., paper is derived from wood but is very different from wood.

Claim 10 is vague and indefinite because it recites "a protein as claimed in claim 5 linked to an antigen, hapten or polysaccharide for eliciting an immune response to said antigen, hapten, or polysaccharide. This is vague and confusing as it is stating basically that the antigen, hapten or polysaccharide would enhance its own immune response. It appears the claim should be amended to recite "for eliciting an immune response to said protein".

Claims 12 and 13 include non-elected species. The claim should be amended so as to refer solely to HMW2.

Claim 13 is vague and indefinite because it refers to an amount of amino acids located in a terminus of a protein, but provides no sequence identifier which places the recited epitope in relation to the entire protein. When a specific domain is identified by amino acid number, the sequence to which it refers must be included in the claims. While the specification can be used to provide definitive support, the claims are not read in a vacuum. Rather, the claim must be definite and complete in and of itself. Limitations from the specification will not be read into the claims. The claims as they stand are incomplete and fail to provide adequate structural properties to allow for one to identify what is being claimed.

Claim Rejections - 35 USC § 112-Deposit requirement

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 5, 7, 10, 11, 12 and 13 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification lacks complete deposit information for the deposit of monoclonal antibodies AD6 and 10C5. Reproduction of an identical cell line and antibody is an extremely unpredictable event. Because it is not clear that the properties of these monoclonal antibodies are known and publicly available or can be reproducibly isolated from nature without undue experimentation and because the best mode disclosed by the specification requires the use of the antibodies, a suitable deposit for patent purposes is required. Exact replication of the monoclonal antibodies is an unpredictable event. The deposit number of the monoclonal antibodies should be included in the claims and needs to be included in the specification (see pages 6 and 7 which contain a blank space after 'ATCC".

If the deposit has been made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by applicant or assignees or a statement by an attorney of record who has authority and control over the conditions of the deposit over his or her signature and registration

number stating that the deposit has been accepted by an International Depository Authority under the provisions of the Budapest Treaty, that all restrictions upon public access to the deposit will be replaced if viable samples cannot be dispensed by the depository is required. This requirement is necessary when deposits are made under the provisions of the Budapest Treaty as the Treaty leaves this specific matter to the discretion of each State. Amendment of the specification to recite the date of the deposit and the complete name and full street address of the depository is required.

If the deposits have not been made under the provisions of the Budapest Treaty, then in order to certify that the deposits comply with the criteria set forth in 37 CFR §1.801-1.809, assurances regarding availability and permanency of deposits are required. Such assurance may be in the form of an affidavit or declaration by applicants or assignees or in the form of a statement by an attorney of record who has the authority and control over the conditions of deposit over his or her signature and registration number averring:

(a) during the pendency of this application, access to the deposits will be afforded to the Commissioner upon request;

(b) all restrictions upon the availability to the public of the deposited biological material will be irrevocably removed upon the granting of a patent on this application;

© the deposits will be maintained in a public depository for a period of at least thirty years from the date of the deposit or for the enforceable life of the patent or for a period of five

years after the date of the most recent request for the furnishing of a sample of the deposited biological material, whichever is longest; and

(d) the deposits will be replaced if they should become non-viable or non-replicable.

In addition, a deposit of the biological material that is capable of self-replication either directly or indirectly must be viable at the time of the deposit and during the term of deposit. Viability may be tested by the depository. The test must conclude only that the deposited material is capable of reproduction. A viability statement for each deposit of a biological material not made under the Budapest Treaty must be filed in the application and must contain:

1)The name and address of the depository;

2)The name and address of the depositor;

3)The date of deposit;

4)The identity of the deposit and the accession number given by the depository;

5)The date of the viability test;

6)The procedures used to obtain a sample if the test is not done by the depository; and

7)A statement that the deposit is capable of reproduction.

As a possible means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of each deposit.

If the deposit was made after the effective filing date of the application for patent in the United States, a verified statement is required from a person in a position to corroborate that the cell line described in the specification as filed is the same as that deposited in the depository.

Corroboration may take the form of a showing of a chain of custody from applicant to the depository coupled with corroboration that the deposit is identical to the biological material described in the specification and in the applicant's possession at the time the application was filed.

Applicant's attention is directed to In re Lundak, 773 F.2d. 1216, 227 USPQ 90 (CAFC 1985) and 37 CFR §1.801-1.809 for further information concerning deposit practice.

Claim Rejections - 35 USC § 112-Enablement

6. Claims 5, 10, 11, 12 and 13 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated and purified high molecular weight protein (HMW3) which is encoded by the nucleotide sequence set forth in SEQ ID NO:3 and which has the amino acid sequence set forth in SEQ ID NO:4, as well as conjugates comprising this protein linked to an antigen, hapten or polysaccharide, does not reasonably provide enablement for the breadth of the other claims, i.e., any HMW protein, fragment or variant which has at least one surface-exposed B-cell epitope and which is recognized by monoclonal antibody AD6, or peptides which are at least six amino acids and no more than 150 amino acids corresponding to at least one protective epitope of HMW3 which is recognized by at least one of monoclonal antibodies AD6 or 10C5 and wherein the epitope is located within the 75 amino acids of the carboxy terminus of HMW2 protein. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The breadth of the instant claims contains proteins and peptides other than what is specified in the sequence disclosure. The specification states that substitutions, additions, or deletions may be made to the defined sequences, i.e., "variants"; however, the specification provides no guidance as to what amino acids may be changed without causing a detrimental effect to the protein to be produced. Further, it is unpredictable as to which amino acids could be removed and which could be added. While it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where amino acid substitutions can be made with a reasonable expectation of success are limited. Other positions are critical to the protein's structure/function relationship, e.g., such as various positions or regions directly involved in binding, catalysis in providing the correct three-dimensional spacial orientation of binding and catalytic sites. These regions can tolerate only very little or no substitutions. Selective point mutation to one key antigen residue eliminate the ability of an antibody to recognize this altered antigen. If the range of decreased binding ability after single point mutation of a protein antigen varies, one could expect point mutations in the protein antigen to cause varying degrees of loss of protection, depending on the relative importance to the binding interaction of the altered residue. Alternatively, the combined effects of multiple changes in an antigenic determinant could again result in loss of protection. A protein having multiple antigenic sites, multiple point mutations, or accumulated point mutations at key residues could create a new antigen that is precipitously or progressively unrecognizable by any of the antibodies in the polyclonal pool. Thus, proteins of different levels of homology may not induce

antibody which is recognized by the "native" HAP on the *H.influenzae* bacteria, and be ineffective in "treating" *H.influenzae* disease.

Applicants have also not identified any specific fragments or variants which could protect against disease caused by a non-typeable *Haemophilus* strain. The location of "protective" epitopes has not been provided. Often it takes more than one epitope to provide protection. Accordingly, claims to synthetic protective epitope(s) , fragments and variants are not enabled. Additionally, there is no correlation that a fragment, peptide or variant which binds monoclonal AD6 or 10C5 is protective. The specification does not provide data which enables claims to fragments "which retain the ability to protect against disease", as the specification does not document the effects of the antibody to the "fragment/peptide/variant" in any *in vitro* or *in vivo* system.

Applicants have provide no guidance to enable one of ordinary skill in the art how to determine, without undue experimentation, the effects of different amino acid substitutions and the nature and extent of the changes that can be made, nor have they identified specification location of epitopes which are protective. Given the lack of guidance contained in the specification and the unpredictability for determining acceptable amino acid substitutions, one of skill in the art could not make or use the broadly claimed invention without undue experimentation.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371© of this title before the invention thereof by the applicant for patent.

8. Claims 5, 7, 10, 11, 12 and 13 are rejected under 35 U.S.C. 102(b) as being anticipated by Barenkamp et al. (WO 94/21290) As stated above, the instant claims only have priority back to 08/617,697 which was filed 4/1/96.

Barenkamp et al disclose isolated and purified high molecular weight proteins (HMW1, HMW2, HMW3 and HMW4) (see abstract and claim 1). All of these proteins would inherently comprise at least one surface-exposed B-cell epitope which is recognized by the AD6 monoclonal antibody, since the AD6 monoclonal antibody is directed to a conserved epitope which all 4 proteins have in common. Variants and fragments of HMW1, HMW2, HMW3 and HMW4, which retain the immunological ability to protect against disease caused by non-typeable *Haemophilus* are also taught (see page 2, lines 11-19). Conjugates of these HMW proteins and fragments to antigens, haptens or polysaccharides are also disclosed (see the paragraph bridging page 5-6).

It is noted that instant claim 5 encompass all HMW proteins. Accordingly, an isolated *Haemophilus* HMW1 or HMW2 protein (which were well known proteins prior to 4/1/96) would anticipate these claims.

9. Claims 5, 10, and 12 are rejected under 35 U.S.C. 102(b) as being anticipated by Barenkamp et al. (Pediatr. Infect. Dis. 9:333-337, 1990) As stated above, the instant claims only have priority back to 08/617,697 which was filed 4/1/96.

Barenkamp et al teach the high molecular weight proteins of NTHi, and a source of antisera which precipitated the protein(s). See at least page 333. these proteins would inherently comprise at least one surface-exposed B-cell epitope which is recognized by the AD6 monoclonal antibody, since the AD6 monoclonal antibody

10. Claims 5, 7, 12 and 13 are rejected under 35 U.S.C. 102(b) as being anticipated by Barenkamp et al. (Pediatric Research, May 1990, Vol. 17 (4 part 2), Abstract 983) or Barenkamp et al. (Pediatric Research, April 1991, Abstract 985). As stated above, the instant claims only have priority back to 08/617,697 which was filed 4/1/96.

Barenkamp et al teach the cloning and expression of genes for nontypeable NTHi high molecular weight outer membrane proteins which are targets of bactericidal antibody. The proteins were isolated and purified. these proteins would inherently comprise at least one surface-exposed B-cell epitope which is recognized by the AD6 monoclonal antibody, since the AD6 monoclonal antibody is directed to a conserved epitope contained within these proteins. Barenkamp teaches a 120kDa protein and a 125kDa protein. This is consistent with the HMW1

and HMW2 proteins. Although the reference does not disclose the amino acid sequence of its 120kDA protein, absent evidence to the contrary, it would inherently be that of SEQ ID NO:4. The mere discovery of an amino acid sequence of an already known and isolated protein does not impart novelty.

It is noted that instant claim 5 encompass all HMW proteins. Accordingly, an isolated *Haemophilus* HMW1 or HMW2 protein (which were well known proteins prior to 4/1/96) would anticipate these claims.

11. Claims 5, 7, 10, 11, 12 and 13 are rejected under 35 U.S.C. 102(e) as being anticipated by Barenkamp et al.(US Patent No. 5,869,065) or Barenkamp et al (US Patent No. 5,549,897).As stated above, the instant claims only have priority back to 08/617,697 which was filed 4/1/96.

Both Barenkamp et al references disclose isolated and purified high molecular weight proteins (HMW1, HMW2, HMW3 and HMW4). All of these proteins would inherently comprise at least one surface-exposed B-cell epitope which is recognized by the AD6 monoclonal antibody, since the AD6 monoclonal antibody is directed to a conserved epitope which all 4 proteins have in common. Variants and fragments of HMW1, HMW2, HMW3 and HMW4, which retain the immunological ability to protect against disease caused by non-typeable *Haemophilus* are also taught. Conjugates of these HMW proteins and fragments to antigens, haptens or polysaccharides are also disclosed.

It is noted that instant claim 5 encompass all HMW proteins. Accordingly, an isolated *Haemophilus* HMW1 or HMW2 protein (which were well known proteins prior to 4/1/96) would anticipate these claims.

Double Patenting

12. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321© may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

13. Claims 5, 7, 12 and 13 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim of U.S. Patent No. 5,549,897. Although the conflicting claims are not identical, they are not patentably distinct from each other because the patented claims recite a vaccine comprising the proteins which are recited in the pending claims. These vaccines are structurally the same as the proteins being claimed because a physiological carrier reads on water or PBS, which would naturally be present in the isolation, natural purification or recombinant production of the claimed proteins.

The term "vaccine" is an intended use only. A recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. A "physiologically acceptable carrier" reads on water and therefore would be inherent in the preparation of the proteins.

14. Claims 5, 7, 12 and 13 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim of U.S. Patent No. 5,869,065. Although the conflicting claims are not identical, they are not patentably distinct from each other because the patented claims recite a vaccine comprising the proteins which are recited in the pending claims. These vaccines are structurally the same as the proteins being claimed because a physiological carrier reads on water or PBS, which would naturally be present in the isolation, natural purification or recombinant production of the claimed proteins.

The term "vaccine" is an intended use only. A recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. A "physiologically acceptable carrier" reads on water and therefore would be inherent in the preparation of the proteins.

15. Claims 10 and 11 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim of U.S. Patent No. 5,876,733. Although the conflicting claims are not identical, they are not patentably distinct from each other because the patented claims recite a slightly broader scope than the conjugates which are recited in the pending claims because they recite that HMW1 or HMW2 may be included in the conjugates. These claims are a genus of the species instantly claimed and therefore they are not patentably distinct from one another. These conjugates are structurally the same as the conjugates being claimed.

16. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15,1989). The Group 1645 Fax number is (703) 308-4242 which is able to receive transmissions 24 hours/day, 7 days/week.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer E. Graser whose telephone number is (703) 308-1742. The examiner can normally be reached on Monday-Friday from 7:00 AM-4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached on (703) 308-3909.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

JGraser 4/1/03

JENNIFER E. GRASER
PRIMARY EXAMINER